to page 14, line 7 of the specification). SNPs, in contrast, were recognized as being potentially suitable for high-resolution genetic analyses, but no one had identified any systematic methods for identifying sets of evenly-spaced, highly heterozygous, ideally-spaced markers that could actually be used to perform such analyses. In view of the very high frequency of SNPs in the genome, such methods were critically needed, as methods of random SNP identification such as those described in Goelet were enormously inefficient, especially for analyses involving a particular genomic region. Therefore, the present invention represented a significant and much-needed advance over the prior art.

The presently-claimed invention provides a method wherein a physical map is generated covering the genome or a portion thereof, and this physical map is used to selectively identify regions for sequencing and SNP identification. In a primary embodiment of the invention, this method involves four steps: obtaining a library of genomic DNA fragments covering all or at least 100kb of a genome, ordering the fragments, determining sequences from selected regions within the fragments, and using these sequences to identify polymorphisms within a population, wherein the polymorphisms have a heterozygosity of at least 0.18 and an inter-marker spacing of less than 50kb.

In contrast, Goelet does not provide a method for selectively identifying SNPs with any desired property, but rather simply teaches the random selection of clones from a genomic library and the subsequent sequencing of all or part of these clones in a plurality of individuals to identify SNPs. Importantly, because of the random nature of this method, this method provides no control over numerous critical aspects of the SNPs identified, including their genomic localization and their inter-marker spacing. This is illustrated in Table 5, where a set of human markers apparently identified using the same methods are shown to be present at widely varying locations throughout the genome: 2p12, 2q3-q21, 2q13-q31, 7q31, and 19p13.3. Such random collections of markers are not useful for high resolution genetic analyses, such as association studies.

Consistent with these important differences between the present methods and those of Goelet, certain of the steps required by the present claims are neither anticipated nor suggested by Goelet. For example, the present method requires that the collection of genomic fragments of step (a) cover all or a portion of the genome comprising "at least 100kb." Although the Examiner interprets this claim limitation as encompassing any collection of fragments that together add up to at least 100kb (meaning that the collection of random fragments assembled by Goelet meets the limitation), this limitation was intended to refer to at least 100kb of *contiguous* genomic DNA. Accordingly, to clarify the claim language, claim 86 has now been amended to read, "at least 100kb *of contiguous genomic DNA*." Therefore, a collection of random clones that represents a total of 100kb but which does not cover any particular 100kb of contiguous genomic DNA, such as those disclosed by Goelet, neither anticipates nor suggests the present claims.

Another claim limitation that is not taught by Goelet concerns step (b) of present claim 86, i.e. "determining the order of said plurality of genomic fragments in the genome." This step is critical to the present method, because this ordering step provides information that allows the identification of sequences suitable for the identification of evenly spaced markers covering the region. By varying the size of the clone inserts as well as the amount of sequence that is examined, it is possible to ensure that a set of markers having a desired heterozygosity and inter-marker spacing is obtained.

In contrast, the methods described in Goelet involve the random selection of sequences from the genome, and do not involve the generation of a physical map (i.e. the preparation and ordering of a collection of clones) as a prelude to, or basis for, the determination of sequences suitable for SNP identification. For example, in Example 1 of Goelet, a horse genomic DNA library was first generated by digesting the genomic DNA and cloning it into a vector. Clone inserts were then randomly selected, sequenced, and examined in a number of individual horses to identify polymorphic markers. In no way does this method include or suggest the ordering of genomic fragments to identify sequences for SNP idenfication. Significantly, the Office Action fails to address this claim limitation, despite the well-established standard that a claim can be anticipated only if each and every element of the claim is present in the cited art (see, e.g., MPEP §2131).

Finally, as noted above, the Examiner's arguments concerning heterozygosity and inter-marker spacing of SNPs are based upon the assertion that the methods of Goelet could be scaled up to identify every SNP in the genome, and that as a result Goelet inherently discloses the present claim limitations addressing these features. Specifically, the Office Action states:

> Goelet et al. do not explicitly teach the heterozygosity rate of claims 82 and 93, however, the heterozygosity rate is that of the SNPs to be identified and are an inherent characteristic of the human DNA being evaluated. Since Goelet et al. fairly teach identifying all SNPs of any animal, including that of humans, the SNPs being identified would have as an inherent property, the heterozygosity rates set forth of claims 86, 92, and 93, and by extension, any claim that depends therefrom. (See, page 4 of the Office Action).

In making this assertion, the Examiner presents no arguments or evidence as to why Goelet's method could be scaled up to identify all SNPs of any animal. Indeed, Applicants submit that it could not. Identifying all SNPs in an animal using a random approach would involve sequencing the entire genome of the animal multiple times for full coverage. Using a random approach would involve the cloning and sequencing of multiple genomes because one would not know whether they were sequencing a clone containing the same sequence included in another clone already sequenced. For complete coverage of the genome, it is well known that enough clones comprising a total amount of genomic DNA equal to multiple

times the size of the genome must be sequenced with the number of clones needed being dependant on the size of the inserts and the size of the genome. In the case of humans, such complete genome sequencing was not accomplished at even a "draft" le vel until more than seven years after the filing date of the Goelet reference. Accordingly, Applicants submit that one of skill in the art would not have been capable of identifying all SNPs in an animal, particularly a human, based on the Goelet reference. In performing all of the methods taught or suggested by Goelet, one would not have performed the steps necessary to meet the limitations of the claims. Accordingly, the Examiner's assertion that Goelet inherently teaches the heterozygosity and inter-marker spacing limitations of the present claims is incorrect, and the present rejection of the claims on this basis is thus improper.

Further, even if the method of Goelet could be scaled up, Goelet provides no motivation or suggestion to do so. On page 16, lines 30-31, for example, Goelet state that to practice their method, only 200-500 clones are purified out of a collection of 50,000 clones of genomic DNA, and SNPs are then identified within the selected clones. Golet teaches nothing about the desirability of examining more than the 200-500 clones. Significantly, sequencing a collection of 200-500 random segments would almost certainly fail to meet the requirements concerning heterozygosity and inter-marker spacing of the present claims. Thus, for the reasons stated above, no one of ordinary skill in the art would have been motivated to use a technique for which they knew ahead of time would not yield the desired result.

As discussed above, numerous of the limitations of the present claims are neither disclosed nor suggested by Goelet. Accordingly, as a rejection under 35 U.S.C. §102 requires that each element of the allegedly-anticipated claim be present in the cited reference, and as a *prima facie* case of obviousness requires both that each and every claim element be present and that a motivation or suggestion exists to combine or modify the elements to achieve the claimed invention, Applicants submit that the present rejections under both §102 and §103 are improper, and respectfully request their withdrawal.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Attached hereto is a clean version of the changes made to the claims by the current amendment, the attached page is captioned "**CLEAN VERSION WITH CURRENTLY PENDING CLAIMS.**"

Conclusions

Applicants respectfully submit that the present application is fully in condition for allowance and such action is earnestly solicited. If any questions remain, the Examiner is cordially invited to contact the undersigned to resolve such questions in a timely manner.

Please charge any additional fees, or credit overpayment to Deposit Account No. 50-1181.

Respectfully submitted,

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Version with markings to show changes made.

86. (Twice amended) A method of obtaining a plurality of single nucleotide polymorphisms comprising the steps of:

(a) obtaining a human nucleic acid library comprising a plurality of genomic DNA fragments containing the full human genome or a portion of the human genome comprising at least 100kb of contiguous genomic DNA;

(b) determining the order of said plurality of genomic DNA fragments in the genome;

(c) sequencing selected regions of said plurality of genomic DNA fragments; and

(d) identifying nucleotides in said selected regions which vary between individuals, thereby defining a set of single nucleotide polymorphisms; wherein said plurality of single nucleotide polymorphisms comprises single nucleotide polymorphisms having a heterozygosity rate of at least about 0.18 and having a mean inter-marker spacing of less than 50kb.

122. (New) A map produced by the method of Claim 86.